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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,142	MILLER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/28/03; 4/29/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,9,32-35,38-43,45 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/29/03* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 are pending.

2. In view of the amendment filed 7/28/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of potentiates the apoptotic effect of photosensitizer such as Lutetium Texaphyrin (Lu-Tex) on endothelial cells in vitro, **does not** reasonably provide enablement for a method of treating unwanted choroidal neovasculature comprising endothelial cells such as age-related macular degeneration by (a) administering to the mammal such as primate and human an anti-angiogenesis factor such as angiostatin or any "anti-vascular endothelial growth factor antibody"; and (b) administering to the mammal an amount of *any* "tetrapyrrole derivative" sufficient to permit an effective amount to localize in the choroidal neovasculature and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature as set forth in claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 for treating age-related macular degeneration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex) used in photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* when compared to angiostatin or Lu-Tex alone (page 24). The effect of Lutetium Texaphyrin (Lu-Tex) on BRCE cells appears to be apoptosis by increases Caspase-3 (page 27). The combination of angiostatin and Lu-Tex/PDT on BRCE cells increases caspase-3 like activity more abruptly and more rapidly as compared to Lu-Tex/PDT alone (page 28). The specification on page 15 defines the term "anti-angiogenesis factor" is any molecule, protein, peptide, nucleic acid (ribose nucleic acid (RNA) or deoxyribose nucleic acid (DNA)), protein/peptide inhibitors peptidyl nucleic acid, organic compound, or inorganic compound, that reduces or inhibits the formation of new blood vessels in a mammal.

The specification does not teach how to effectively treat unwanted choroidal neovasculature such as associated with age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, *any* idiopathic disorders, choroiditis, choroidal rupture, overlying choroids nevi and any inflammatory diseases by administering *any* anti-angiogenesis factor and *any* photosensitizer mentioned above in any mammal. There is no guidance for the binding specificity of any "anti-vascular endothelial growth factor antibody" that can be used for the claimed method. There is insufficient guidance as to which cell in the choroidal neovasculature that secretes vascular endothelial growth factor (VEGF), in turn, the antibody to VEGF could block the binding of said VEGF to which VEGF receptor given that there are many VEGF receptors exist in nature and not all VEGF receptors are expressed in the chroidal vasculature. Since the antibody to VEGF that binds to the VEGF receptor is not specific, it is not clear how administering the undisclosed "tetrapyrrole derivative" could then be irradiate with laser to occlude the chroidal vasculature.

As to "tetrapyrrole derivative" in claims 1, 33, and 41, the term "derivative" does not convey a specific structure such as amino acid sequence, or chemical structure. Given the indefinite number of undisclosed "tetrapyrrole derivative", there is insufficient guidance as to which undisclosed "tetrapyrrole derivative" that has special absorption property to permit deep tissue penetration and rapid clearance and is effective for the claimed method, not to mentioned having synergistic effects compared to either "tetrapyrrole derivative" alone or anti-VEGF antibody or angiostatin alone.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion

which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Further, the specification does not teach how to extrapolate data obtained from in vitro proliferation and apoptosis assays to the development of effective in vivo human therapeutic compositions as a method of treating any unwanted choroidal neovasculature, any inflammatory disorders, idiopathic disorders and age-related macular degeneration that differ with respect to etiology and treatment endpoints commensurate in scope with the claimed invention.

Even if the anti-angiogenesis factor is limited to angiostatin and the photosensitizer is limited to lutetium texaphyrin, there are no in vivo working examples in the specification as filed demonstrating that the combination of angiostatin and lutetium texaphyrin is effective for treating any unwanted choroidal neovasculature associated with *any* idiopathic disorder, and *any* inflammatory disease, much less age-related macular degeneration. A method of treating any disease in the absence of in vivo data is unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Given the indefinite number of undisclosed "tetrapyrrole derivative" and the lack of guidance as to the binding specificity of the antibody in the claimed method, it is unpredictable which undisclosed "tetrapyrrole derivative" in combination with either angiostatin or anti-VEGF antibody would be useful as a method for treating unwanted choroidal neovasculature associated with age-related macular degeneration, let alone any idiopathic disorders, and any inflammatory diseases.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/9/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims have been amended to require the use of a specific angiogenesis factor, for example, angiostatin, and an anti-vascular endothelial growth factor antibody and a certain class of photosensitizer, for example a tetrapyrrole derivative photosensitizer. (2) the art such as US patent no. 5,767,986 shows that prior to the filing date of instant application, it had been possible to selectively occlude CNV in primate eyes using green porphyrin-based PDT. (3) The specification on page 9 lines 12-29 discuss exemplary terapyrrole derivative photosensitizers are useful in the practice of the claimed invention. (4) The antiangiogenesis factor useful in the practice of the claimed invention is discussed on page 16 of the application. (5) The courts have long held that there is no magical relationship between the number of representative examples and the breadth of the claims.

However, amended claims still recite any "tetrapyrrole derivative" for the claimed method. The term "derivative" does not convey a specific structure such as amino acid sequence, or chemical structure. The specification discloses only one exemplary terapyrrole derivative Lutetium Texaphyrin (Lu-Tex) photosensitizer. The specification discloses pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex) used in photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* when compared to angiostatin or Lu-Tex alone (page 24). The effect of Lutetium Texaphyrin (Lu-Tex) on BRCE cells appears to be apoptosis by increases Caspase-3 (page 27). The combination of angiostatin and Lu-Tex/PDT on BRCE cells increases caspase-3 like activity more abruptly and more rapidly as compared to Lu-Tex/PDT alone (page 28). The specification does not teach how to make and use other tetrapyrrole derivative for the treating unwanted choroidal neovascular disease. Given the indefinite number of undisclosed "tetrapyrrole derivative", there is insufficient guidance as to which undisclosed "tetrapyrrole derivative" that has special absorption property to permit deep tissue penetration and rapid clearance and is effective for the claimed method, not to mentioned having synergistic effects compared to either "tetrapyrrole derivative" alone or anti-VEGF antibody or angiostatin alone.

With regard to anti-antiangiogenesis factor such as anti-VEGF antibody useful in the practice of the claimed invention, there is no guidance for the binding specificity of said "anti-vascular endothelial growth factor antibody" that can be used for the claimed method. There is insufficient guidance as to which cell in the choroidal neovasculature that secretes vascular endothelial growth factor (VEGF), in turn, the antibody to VEGF could block the binding of said VEGF to which VEGF receptor, given that there are more than one VEGF receptors exist in nature and not all VEGF receptors are expressed in the chroidal vasculature in the eye. Since the antibody to VEGF that binds to the VEGF receptor is not specific, it is not clear how administering the undisclosed "tetrapyrrole derivative" could then be irradiate with laser to occlude the chroidal vasculature. Even if the anti-angiogenesis factor is limited to angiostatin and the photosensitizer is limited to lutetium texaphyrin, there are no in vivo working examples in the specification as filed demonstrating that the combination of angiostatin and lutetium texaphyrin is effective for treating any unwanted choroidal neovasculature associated with *any* idiopathic disorder, and *any* inflammatory disease, much less age-related macular degeneration. For these reasons, it would require an undue amount of experimentation for one of skill in the art to practice the claimed invention. the claimed invention.

5. Claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of treating unwanted choroidal neovasculature comprising endothelial cells such as age-related macular degeneration by (a) administering to the mammal such as primate and human an anti-angiogenesis factor such as angiostatin or *any* "anti-vascular endothelial growth factor antibody"; and (b) administering to the mammal an amount of *any* "tetrapyrrole derivative" sufficient to permit an effective amount to localize in the choroidal neovasculature and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature as set forth in claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 for treating age-related macular degeneration.

The specification discloses only one exemplary terapyrrole derivative Lutetium Texaphyrin (Lu-Tex) photosensitizer. Further, the specification discloses only pre-treating

bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex)/photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* when compared to angiostatin or Lu-Tex alone (page 24). The effect of Lutetium Texaphyrin (Lu-Tex) on BRCE cells appears to be apoptosis by increases Caspase-3 (page 27). The combination of angiostatin and Lu-Tex/PDT on BRCE cells increases caspase-3 like activity more abruptly and more rapidly as compared to Lu-Tex/PDT alone (page 28). The specification on page 15 defines the term "anti-angiogenesis factor" is any molecule, protein, peptide, nucleic acid (ribose nucleic acid (RNA) or deoxyribose nucleic acid (DNA)), protein/peptide inhibitors peptidyl nucleic acid, organic compound, or inorganic compound, that reduces or inhibits the formation of new blood vessels in a mammal.

With the exception of the specific method of pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex)/photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* using Texaphyrin (Lu-Tex) as the photosensitizer, and angiostatin as the antiangiogenesis factor, there is insufficient written description about the structure associated with function of *any* anti-angiogenesis factor such as any anti-VEGF antibody and any tetrapyrrole derivatives as recited in claims 1, 33, and 41for a method of treating unwanted choroidal neovasculature or ameliorates the symptoms of any disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streak, *any* idiopathic disorders, choroiditis, choroidal rupture, overlying choroids nevi, and *any* inflammatory disease.

Further, Applicant discloses the use of only one specific anti-angiogenic factor such as angiostatin and one specific photosensitizer such as lutetium texaphyrin for in vitro method of inhibiting endothelial cells growth. Given the lack of a written description of *any* additional representative species of terapyrrole derivative and anti-vascular endothelial growth factor antibody for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/9/01 have been fully considered but are not found persuasive.

Applicants' arguments filed 2/9/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims have been amended to require the use of a specific angiogenesis factor, for example, angiostatin, and an anti-vascular endothelial growth factor antibody and a certain class of photosensitizer, for example a tetrapyrrole derivative photosensitizer. (2) the art such as US patent no. 5,767,986 shows that prior to the filing date of instant application, it had been possible to selectively occlude CNV in primate eyes using green porphyrin-based PDT. (3) The specification on page 9 lines 12-29 discuss exemplary terapyrrole derivative photosensitizers are useful in the practice of the claimed invention. (4) The antiangiogenesis factor useful in the practice of the claimed invention is discussed on page 16 of the application.

However, amended claims still recite any "tetrapyrrole derivative" for the claimed method. The term "derivative" does not convey a specific structure such as amino acid sequence, or chemical structure. The specification discloses only one exemplary terapyrrole derivative Lutetium Texaphyrin (Lu-Tex) photosensitizer. The specification discloses pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex) used in photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* when compared to angiostatin or Lu-Tex alone (page 24). The effect of Lutetium Texaphyrin (Lu-Tex) on BRCE cells appears to be apoptosis by increases Caspase-3 (page 27). The combination of angiostatin and Lu-Tex/PDT on BRCE cells increases caspase-3 like activity more abruptly and more rapidly as compared to Lu-Tex/PDT alone (page 28). The specification does not teach how to make and use other tetrapyrrole derivative for the treating unwanted choroidal neovascular disease. Given the indefinite number of undisclosed "tetrapyrrole derivative", there is inadequate written description about the undisclosed "tetrapyrrole derivative" that has special absorption property to permit deep tissue penetration and rapid clearance and is effective for the claimed method, not to mentioned having synergistic effects compared to either "tetrapyrrole derivative" alone or anti-VEGF antibody or angiostatin alone.

With regard to anti-antiangiogenesis factor such as anti-VEGF antibody useful in the practice of the claimed invention, there is inadequate written description for the binding specificity of said "anti-vascular endothelial growth factor antibody" that can be used for the

claimed method. Further, there is inadequate written description about which cell in the choroidal neovasculature that secretes vascular endothelial growth factor (VEGF), in turn, the antibody to VEGF could block the binding of said VEGF to which VEGF receptor, given that there are more than one VEGF receptors exist in nature and not all VEGF receptors are expressed in the chroidal vasculature in the eye. Since the antibody to VEGF that binds to the VEGF receptor is not specific, it is not clear how administering the undisclosed anti-VEGF antibody and "tetrapyrrole derivative" could then be irradiate with laser to occlude the chroidal vasculature. Even if the anti-angiogenesis factor is limited to angiostatin and the photosensitizer is limited to lutetium texaphyrin, there are no in vivo working examples in the specification as filed demonstrating that the combination of angiostatin and lutetium texaphyrin is effective for treating any unwanted choroidal neovasculature associated with *any* idiopathic disorder, and *any* inflammatory disease, much less age-related macular degeneration. Finally, Applicant discloses the use of only one specific anti-angiogenic factor such as angiostatin and one specific photosensitizer such as lutetium texaphyrin for in vitro method of inhibiting endothelial cells growth. Given the lack of a written description of *any* additional representative species of terapyrrole derivative and anti-vascular endothelial growth factor antibody for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-4, 6, 8-9, 32-35, 38-43, 45, and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,162,242 (Dec 2000, PTO 892) in view of US Pat No 5,733,876 (March 1998, PTO 892).

The '242 patent teaches a method of treating unwanted choroidal neovasculature such as proliferation of new blood vessels in the subretinal area of the eyes associated with macular degeneration or neoplastic cells by administering an agent such as adenosine diphosphate (ADP) to enhance thrombus formation prior to administering to the mammal such as human an amount of various photosensitizer such as ethyletiopurpurin, protoporphyrin, aminolevulinic acid which is an amino-derivative, benzoporphyrin derivative, Lutex (Lutetium texaphyrin) which is a tetrapyrrode derivative (See column 5, lines 5-51, column 8, lines 59-60, claims 1, 13-18 of the '242 patent, in particular) and irradiating the choroidal neovasculature with a laser light such that the light absorbance wavelength is around 630 nm to 732 nm absorbed by the photosensitizer so as to occlude the choroidal neovasculature (See column 8, lines 48-60, in particular). The benefits of the reference method are (1) it selectively destroying the neovascular tissue while radiation-induced damage to normal tissues and vessels is minimized or prevented (See column 6, lines 25-28, in particular).

The claimed invention differs from the teaching of the reference only that the method comprises administering to the mammal an anti-angiogenesis factor such as angiostatin.

The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the coagulation factor in the method of treating unwanted choroidal neovasculature as taught by the '242 patent for the angiostatin as taught by the '876 patent for a method of treating unwanted choroidal neovasculature as taught by the '242 patent and the '876 patent. From the combined teachings of the references, it is apparent that one

of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '876 patent teaches angiostatin is useful for a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration and angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular). The '242 patent teaches photosensitizer in combination with coagulation factor are useful for treating unwanted choroidal neovasculature such as proliferation of new blood vessels in the subretinal area of the eyes associated with macular degeneration and the benefits of photodynamic therapy using photosensitizer is that it selectively destroyed the neovascular tissue while radiation-induced damage to normal tissues and vessels is minimized or prevented (See column 6, lines 25-28, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). The recitation of wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (B) and (c) is an obvious results of the combined references teachings.

Applicants' arguments filed 2/9/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) citing references which merely indicate the isolated elements in the claims is not a sufficient basis for concluding that the combination would been obvious. (2) The '242 patent discloses a method of performing PDT, the method involves administering a photosensitizer. The method of '242 patent may also include the use of a vessel occluding agent such as adenosine diphosphate. However, the '242 patent does not teach or suggest combining the PDT method with an anti-angiogenesis factor. (3) The '876 patent discloses using angiostatin to inhibit angiogenesis and to inhibit endothelial cell proliferation. The '876 patent, however, fails to teach or suggest the including angiostatin in a PDT method for treating unwanted CNV. (4) Even if such as a combination were to be made, the skilled artisan would have no reasonable expectation that such a method would be effective at occluding CNV. (5) Applicants submit that the agents that promote the formation of thrombi or clots as discussed

in the '242 patent (for example, adenosine diphosphate) are completely different both in structure and function to angiostatin as discussed in the '876 patent. In contrast, angiostatin as discussed in the '576 patent blocks the growth of new blood vessels. Given that these two are completely different physiological effects, Applicants submit there is no reason for the skilled artisan to believe that anti-angiogenesis agent which acts to inhibit the growth of new blood vessels, would be useful at occluding already existing blood vessels, as required by the teachings of the '242 patent. (6) There is no teaching or suggestion in the applied references that would provide the skilled artisan with a reasonable expectation that a PDT-based method when combined with an-angiogenesis factor would be effective in treating CNV. (7) There is nothing that would suggest that the combined method would be more effective than the sum of each of the separate treatments of PDT and the administration of anti-angiogenesis factor.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, both the '242 patent and the '876 patent teach a method of treating unwanted neovasculature associated with age-related macular degeneration resulting from formation of new blood vessel (choroidal neovasculature), and subretinal hemorrhage. The '242 patent teaches a method of treating unwanted choroidal neovasculature such as proliferation of new blood vessels in the subretinal area of the eyes associated with macular degeneration or neoplastic cells by administering an agent such as adenosine diphosphate (ADP) to enhance thrombus formation or to coagulate blood subretinal hemorrhage prior to administering to the mammal such as human an amount of various photosensitizer such as Lutex (Lutetium texaphyrin) which is a tetrapyrrode derivative (See column 5, lines 5-51, column 8, lines 59-60, claims 1, 13-18 of the '242 patent, in particular) and irradiating the choroidal neovasculature with a laser light such that the light absorbance wavelength is around 630 nm to 732 nm absorbed by the photosensitizer so as to occlude the choroidal neovasculature (See column 8, lines 48-60, in particular). The benefits of the reference

method are (1) it selectively destroying the neovascular tissue while radiation-induced damage to normal tissues and vessels is minimized or prevented (See column 6, lines 25-28, in particular). The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with age-related macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to do this because each of step which is taught by the prior art to be useful for the same purpose, that is, treating unwanted choroidal neovasculature associated with aged related macular degeneration that is characterized by subretinal hemorrhage, and formation of new vessels (choroidal neovasculature). The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

In contrast to applicant's continued assertions that there is no reason for the skilled artisan to believe that anti-angiogenesis agent which acts to inhibit the growth of new blood vessels, would be useful at occluding already existing blood vessels, as required by the teachings of the '242 patent, the combined teachings of the '242 patent and the '876 patent provide clear direction, motivation and expectation of success in treating unwanted choroidal neovasculature using the specific tetrapyrrole derivative and the specific anti-angiogenesis factor.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

Applicant's reliance on unexpected results does not overcome clear and convincing evidence of obviousness. There is insufficient evidence that the method in the instant claims

would differ in an unexpected manner from those described in the references. In the absence of unexpected results (objective evidence), applicant's arguments were not found persuasive.

9. Claims 1-6, 8-9, and 32-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,707,986 (Jan 1998, PTO 892) or US Pat No 6,270,749 B1 (Aug 2001, PTO 892) each in view of US Pat No 5,733,876 (March 1998, PTO 892).

The '986 patent teaches a method of treating unwanted choroidal neovasculature such as formation of new blood vessel in the eyes associated with age-related macular degeneration of a mammal such as living primates and human comprising administering to the mammal an amount of tetrapyrrole derivative photosensitizer such as green porphyrins or benzoporphyrin derivatives (BPD) sufficient to permit an effective amount to localize in the choroidal neovasculature and irradiating the choroidal neovasculature with laser light such as 692 nm of light from argon/dye laser (See column 7, lines 39-42, claims 1-6 of '986 patent, in particular).

The '749 patent teaches the use of photosensitizer such as texaphyrin complex with a diamagnetic metal such as Lutetium which is a tetrapyrrode derivative (See Abstract, column 8, lines 5-17, in particular) for a method of treating age-related macular degeneration (See column 23, lines 6-11, in particular). The '749 patent teaches the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular).

The claimed invention differs from the teachings of the references only that the method comprises administering to the mammal an anti-angiogenesis factor, angiostatin.

The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include angiostatin as taught by the '876 patent for a method of treating

unwanted choroidal neovasculature comprising administering to the mammal an anti-angiogenesis factor such as angiostatin and photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature and irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '876 patent teaches angiostatin is useful for a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration and angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular). The '986 patent teaches photosensitizer such as green porphyrins or benzoporphyrin derivatives (BPD) is effective as a method of treating unwanted choroidal neovasculature associated with age-related macular degeneration of a mammal such as living primates and human (See column 7, lines 39-42, claims 1-6 of '986 patent, in particular). The '749 patent teaches photosensitizer such as Lutetium texaphyrin is effective as a method of treating unwanted choroidal neovasculature associated with age-related macular degeneration because the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). The recitation of wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (B) and (c) is an obvious results of the combined references teachings.

Applicants' arguments filed 2/9/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended. (2) There is no teachings or suggestion in the applied references that suggest their combination, (3) There is no reasonable expectation of success for such combination to be made, (4) Applicants submit that the claimed invention has unexpected properties that would not have been foreseeable by the skilled artisan at the time the invention was made. (5) The '986 patent discloses a PDT method employing a green porphyrin dye for treatment of unwanted CNV. The '749 patent discloses a PDT method employing a texaphyrin dye for the treatment of CNV. Neither the '986 patent nor the '749 patent teach, suggest or in any way infer combining their respective PDT methods with an antiangiogenesis. The '876 patent discloses using angiostatin to inhibit angiogenesis and to inhibit endothelial cell proliferation. The '876 patent, however, fails to teach or suggest the including angiostatin in a PDT method for treating unwanted CNV.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the '986 patent teach a method of treating CNV such as age-related macular degeneration that is characterized by subretinal hemorrhage employing tetrapyrrole derivative such as green porphyrins or benzoporphyrin derivatives (BPD). The '749 patent teach a method of treating CNV such as age-related macular degeneration that is characterized by subretinal hemorrhage employing tetrapyrrole derivative such as Lutetium for a method of treating age-related macular degeneration (See column 23, lines 6-11, in particular). The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to do this because

each of step which is taught by the prior art to be useful for the same purpose, that is, treating unwanted choroidal neovasculature associated with aged related macular degeneration characterized by subretinal hemorrhage, and formation of new vessels (choroidal neovasculature). The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

In contrast to applicant's continued assertions that there is no expectation of success, the combined teachings of the '986 patent, the '749 patent and the '876 patent provide clear direction, motivation and expectation of success in treating unwanted choroidal neovascularature using the specific tetrapyrrole derivative and the specific anti-angiogenesis factor.

In response to applicant's argument that the claimed invention has unexpected properties that would not have been foreseeable by the skilled artisan at the time the invention was made, there is insufficient evidence that the method in the instant claims would differ in an unexpected manner from those described in the references. In the absence of unexpected results (objective evidence), applicant's arguments were not found persuasive.

10. The following new ground of objection is necessitated by the amendment filed 7/28/03.

11. claims 1, 32 and 41 are objected to for reciting non-elected embodiment, anti-vascular endothelial growth factor antibody.

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
Technology Center 1600
November 25, 2003

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